Research Paper

Reduced salience and default mode network activity in women with anorexia nervosa

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Background: The neurobiology of anorexia nervosa is poorly understood. Neuronal networks contributing to action selection, self-regulation and interoception could contribute to pathologic eating and body perception in people with anorexia nervosa. We tested the hypothesis that the salience network (SN) and default mode network (DMN) would show decreased intrinsic activity in women with anorexia nervosa and those who had recovered from the disease compared to controls. The basal ganglia (BGN) and sensorimotor networks (SMN) were also investigated. **Methods:** Between January 2008 and January 2012, women with restricting-type anorexia nervosa, women who recovered from the disease and healthy control women completed functional magnetic resonance imaging during a conditioned stimulus task. Network activity was studied using independent component analysis. **Results:** We studied 20 women with anorexia nervosa, 24 recovered women and 24 controls. Salience network activity in the anterior cingulate cortex was reduced in women with anorexia nervosa (p = 0.030; all results false-discovery rate–corrected) and recovered women (p = 0.039) compared to controls. Default mode network activity in the precuneus was reduced in women with anorexia compared to controls (p = 0.023). Sensorimotor network activity in the supplementary motor area (SMA; p = 0.008), and the left (p = 0.028) and right (p = 0.002) postcentral gyrus was reduced in women with anorexia compared to controls; SMN activity in the SMA (p = 0.019) and the right postcentral gyrus (p = 0.008) was reduced in women with anorexia compared to recovered women. There were no group differences in the BGN. **Limitations:** Differences between patient and control populations (e.g., depression, anxiety, medication) are potential confounds, but were included as covariates. **Conclusion:** Reduced SN activity in women with anorexia nervosa and recovered women could be a trait-related biomarker or illness remnant, altering the drive to approach food. The alterations in the DMN and SMN observed only in women with anorexia nervosa suggest state-dependent abnormalities that could be related to altered interoception and body image in these women when they are underweight but that remit following recovery.

Introduction

Anorexia nervosa is an illness characterized by refusal to maintain a healthy body weight, a distorted view of body shape and severe fear of weight gain.[1] While the neurobiological mechanisms underlying anorexia nervosa are not well understood, neuroimaging studies have found altered brain activation in brain regions contributing to reward and anxiety processing in individuals with anorexia nervosa.[2–11] Such alterations could be involved in the pathologic drive to eat in these individuals.[6,8]

To gain a clearer understanding of neurobiological mechanisms involved in anorexia nervosa, it is important to understand the functionality of the brain networks that underlie illness behaviour. The focus of this study was to investigate intrinsic network activity in women with anorexia nervosa, women recovered from anorexia nervosa and healthy control women to determine if there are differences in brain circuit functionality related to disease state or possible trait abnormalities. Brain intrinsic network activity, measured either in the resting state or across tasks, reflects the basic functional organization of brain networks.[12–14] Although studies are often conducted in the resting state, studies have also assessed intrinsic network activity across task performance,[12–17] which is perhaps more relevant to everyday behaviour. Previous studies have suggested that such task engagement does

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not affect underlying brain activity, but rather that task-related activity is additive.[14,18] Indeed, a study examining a large database of functional magnetic resonance imaging (fMRI) activation studies found functionally connected brain networks identified in the resting state and across tasks to be remarkably similar.[19]

The present study examined network activity across task conditions, which may be relevant to everyday situations, including decision-making and food choice, and could have important implications for behaviour typical in people with anorexia nervosa. We were specifically interested a priori in the default mode network (DMN) and the salience network (SN) based on the relevance of these networks to psychiatric disorders and food-related behaviours. The SN is involved in assessing the relevance of and orienting to internal and external stimuli to support behaviour choice, primarily processed in the anterior cingulate cortex (ACC) and insula.[20,21] The DMN is thought to be involved in self-relevant mentalizing and interoception[22] and includes the posterior cingulate cortex; cuneus/precuneus; and the medial prefrontal, medial temporal and inferior parietal cortices.[22]

Alterations in SN and DMN activity have been observed in patients with other psychiatric disorders, including autism,[23] schizophrenia,[16,24] attention-deficit/hyperactivity disorder,[25,26] Alzheimer disease,[27,28] depression[29,30] and anxiety.[31,32] Brain regions comprising SN and DMN networks, including the insula,[6,10] ACC,[2,4,6,10] precuneus,[33,34] inferior parietal cortex[2,4,10] and medial prefrontal cortex,[2,4] frequently have been found to be altered in people with anorexia nervosa. Relevant to food-related behaviours, previous studies have found increased SN and DMN activity in obese individuals, both at rest and across task performance.[35–37]

A small number of previous studies have investigated functional connectivity in people with anorexia nervosa, although, to our knowledge, ours is the first study to investigate the DMN and SN in currently ill women and to compare activity in these networks between ill and recovered women. Favaro and colleagues[38] found decreased activity in the ventral visual network in people with anorexia nervosa and those recovered from the disease compared with controls, but they also found increased activity in the somatosensory network in those with anorexia nervosa. Cowdrey and colleagues[39] did not study currently ill women, but they found that recovered women showed increased activity within the DMN compared with controls. Kim and colleagues[10] found distinct patterns of connectivity between the insula and frontal regions of the brain among participants with anorexia nervosa, bulimia nervosa and control participants across a visual food cue task. In addition, Amianto and colleagues[40] recently found alterations in connectivity patterns within the cerebellum in participants with anorexia nervosa and bulimia nervosa compared with controls. To our knowledge, the present study is the first to investigate the SN and DMN in women with anorexia nervosa and those recovered from the disease, which could provide insight regarding state- versus trait-related network effects.

We previously investigated task-related brain activity in the same currently ill anorexia nervosa and control groups as those included in the present study in comparison to obese individuals. We found opposite functional brain response in women with anorexia nervosa compared with obese individuals,[8] suggesting opposite brain pathology. As previous studies have found increased intrinsic DMN activity in obese individuals, we hypothesized that DMN activity in women with anorexia nervosa would be reduced and thus opposite to that seen in obesity.[35,37] Based on the findings of Cowdrey and colleagues, who showed increased DMN activity in individuals recovered from anorexia nervosa, we hypothesized that altered DMN activity is dependent on illness state and that reduced activity would be observed only in women with anorexia nervosa compared with controls. To our knowledge, no previous studies have investigated SN activity in women with anorexia nervosa or recovered women, but based on previous findings of increased SN activity in an obese sample,[36] we hypothesized that we would observe reduced SN activity in women with anorexia nervosa. Again, if a decrease in intrinsic network activity were dependent on illness state, we hypothesized that women with anorexia nervosa would show reduced SN activity, but that recovered women would not. In addition to these a priori networks of interest, we also conducted exploratory analyses in networks strongly activated by the task during which these data were recorded, including the basal ganglia (BGN) and sensorimotor networks (SMN).

Methods

Participants

Women with restricting-type anorexia nervosa, women who recovered from restricting-type anorexia nervosa and healthy control women participated in the study. Anorexia nervosa was defined as weight below 85% of that expected based on age and height, severe fear of gaining weight, body image distortion and lack of a menstrual cycle.[41] We excluded women from the study if they had a binge eating/purging type of anorexia. Women in the anorexia nervosa group were within 1–2 weeks of either inpatient or partial hospitalization treatment. To be included in the recovered group, women had to have a history of restricting-type anorexia nervosa, but must have maintained a healthy weight based on height (body mass index [BMI] above 18.5), a normal menstrual cycle and normal exercise habits and food intake for at least 1 year. We recruited control women through advertisements in the Denver metropolitan area, and they were age-matched to patients. A doctoral-level interviewer (G.K.W.F.) confirmed the presence of psychiatric diagnoses, including anorexia nervosa (or the absence of psychiatric disorders in controls), using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition.[42] All participants provided informed consent and procedures were approved by the Colorado Multiple Institutional Review Board.

Behavioural measurements

Participants completed the following questionnaires: Beck Depression Inventory (BDI),[43] State Trait Anxiety Inventory (STAI),[44] Harm Avoidance (Temperament and Character

Inventory),[45] the Intolerance of Uncertainty (IU) Scale,[46] Body Dissatisfaction/Drive for Thinness from the Eating Disorder Inventory-2 (EDI-2)[47] and the Revised Sensitivity to Reward and Punishment Questionnaire.[48]

Experimental design

The imaging studies were performed on a GE 3.0 T MRI scanner. Scanning details can be found in the Appendix, available at jpn.ca. Functional MRI was performed while participants received taste stimuli as part of a conditioned stimulus task (see the Appendix), which has been described previously.[8] In brief, participants learned to associate abstract pictures as conditioned stimuli with the delivery of sucrose or control solution (unconditioned stimuli), and at times there was unexpected receipt or omission of the sucrose taste sample. In this case, the prediction of the reward stimulus was violated, causing a so-called "prediction error." All women with anorexia nervosa and control women involved in the present study were also included in this prior publication,[8] which focused on task-related activation during different reward conditions in comparison to obese individuals. The recovered group in the present study was not included in the previous publication. For the intrinsic network analysis in the present study, data were collapsed across task conditions.

Functional MRI data analyses

Data were preprocessed and analyzed using SPM8 software (Wellcome Department of Imaging Neuroscience). Preprocessing details are described in the Appendix. We conducted a group independent component analysis (ICA) using the GIFT toolbox (http://icatb.sourceforge.net). Data for all participants (across all 3 groups) were processed together. Details are described in the Appendix. Briefly, we identified DMN and SN components based on spatial correlation to DMN and SN masks. Components for all participants, as *z* score maps, were evaluated across the entire brain on a voxel-wise basis with directional contrasts in a 1-way analysis of variance (ANOVA) in SPM8. The SPM8 design matrix included the following covariates, each of which was entered as a separate vector: age, BMI, depression (BDI score), anxiety (STAI score: State) and use of psychiatric medication, coded as 1 or 0 (yes/no). We conducted secondary analyses to ascertain that the inclusion of covariates did not affect result directionality. First, we repeated analyses without the medication covariate, as no control participants were taking psychiatric medications. Second, we repeated analyses without any covariates to determine if inclusion of covariates overall influenced results. We performed an additional exploratory analysis to examine how each network was modulated by task conditions (see the Appendix).

Behavioural and structural data analyses

Group comparisons of participant characteristics and behavioural measures were assessed using 1-way ANOVA in SPSS, as described in the Appendix. As previous studies have found reduced grey matter volume in people with anorexia nervosa,[49] we analyzed structural data to test if group volumetric differences might have influenced functional differences (additional details are available in the Appendix).

Results

Participants

Twenty women with anorexia, 24 recovered women and 24 controls participated in the study. None had a lifetime history of bulimia or reported having previous binge and purge behaviours. Women in the anorexia group were younger, had fewer years of education and had a lower BMI than women in both the recovered and control groups. Participant demographic and behavioural characteristics are summarized in Table 1.

Behavioural measures

Women in the anorexia group scored higher on BDI, Harm Avoidance and IU measures than women in both the recovered and control groups; recovered and control women did not differ significantly from each other. The EDI-2 scores showed that women with anorexia nervosa and recovered women had greater body dissatisfaction and drive for thinness than controls and that women with anorexia nervosa had a significantly greater drive for thinness than recovered women. Women with anorexia and recovered women had higher anxiety scores than controls. In addition, women with anorexia and recovered women had greater sensitivity to punishment than controls, women with anorexia had greater sensitivity to punishment than recovered women, and women with anorexia had greater sensitivity to reward than controls.

Functional MRI data

In the SN, women with anorexia nervosa showed significantly decreased activity compared with controls in the ACC (Table 2 and Fig. 1A), as did recovered compared with control women (Fig. 1B). Activity across all groups is shown in Fig. 2A. Because results indicated potential outliers, we investigated this using the Grubbs test for outliers[50] on the extracted local maxima data in the ACC, and we found 1 significant outlier in the control group. To determine whether this was driving group effects, we performed analyses excluding the outlier. As group effects were not altered, this participant was not excluded. Secondary analyses investigated group effects with the same model excluding the medication covariate and with no covariates. Results were similar (Table 2).

In the DMN (Fig. 3), women with anorexia showed significantly decreased activity compared with controls in the precuneus (Table 2), but there were no significant differences between controls and recovered women. Activity across all groups is shown in Fig. 2B. No significant outliers were detected in the extracted precuneus local maxima data. Secondary analyses revealed similar group effects when excluding the medication covariate and when excluding all covariates (Table 2).

In the BGN, no models revealed significant group differences.

In the SMN, women with anorexia showed significantly decreased activity compared with controls in the left postcentral gyrus (LPG), right postcentral gyrus (RPG) and supplementary motor area (SMA; Table 2 and Fig. 4A). Women with anorexia also showed significantly decreased activity in the RPG and SMA compared with recovered women (Fig. 4B). Recovered women showed marginally decreased activity in the LPG compared with controls. When taking the effects of medication use and all covariates out of the model, results were similar (Table 2). Activity across all groups is shown in Fig. 5. We found 1 significant outlier in recovered women for the SMA local maxima. We repeated our analyses excluding this participant. As no effects were altered, we did not exclude this participant from our analysis.

No group differences in grey matter, white matter or total intracranial volume were observed in the intrinsic network regions that distinguished the groups in this study, suggesting that results are unlikely to be related to structural abnormalities. We performed an exploratory analysis of the β weights derived from temporal sorting in GIFT to identify how each network was modulated by task condition. Results from this analysis are described in the Appendix. Briefly, there were differences among conditions in each network of interest within each group, but there were no significant group differences.

Table 1: Participant demographic characteristics and behavioural data

	Group; mean ± SD*			ANOVA		
Characteristic	Anorexia nervosa, $n = 20$	Recovered, $n = 24$	Control, $n = 24$	F	p value	Comparison
Age, yr	22.85 ± 5.74	30.25 ± 8.13	27.42 ± 6.28	6.41	0.003	Recovered > anorexia nervosa‡ Control > anorexia nervosa†
Age at onset, yr	16.15 ± 2.56	16.63 ± 2.43	—	0.40	0.53	
Education, yr	14.40 ± 2.39	16.87 ± 2.74	16.62 ± 2.06	6.75	0.002	Recovered > anorexia nervosa‡ Control > anorexia nervosa‡
Illness duration, yr	6.76 ± 6.23	5.90 ± 5.21	—	0.25	0.62	
Recovery duration, yr	—	7.90 ± 6.01	—	—	—	
Body mass index	16.03 ± 1.07	20.83 ± 2.37	21.64 ± 1.26	67.37	< 0.001	Recovered > anorexia nervosa§ Control > anorexia nervosa§
BDI	24.57 ± 10.45	4.50 ± 4.21	1.12 ± 0.95	84.94	< 0.001	Anorexia nervosa > recovered§ Anorexia nervosa > control§
STAI	50.30 ± 9.44	44.96 ± 9.41	32.67 ± 11.79	17.25	< 0.001	Anorexia nervosa > control§ Recovered > control§
Harm avoidance	24.00 ± 5.40	15.54 ± 6.47	9.58 ± 3.99	39.25	< 0.001	Anorexia nervosa > recovered§ Anorexia nervosa > control§
Reward sensitivity	7.20 ± 3.72	5.83 ± 3.25	4.42 ± 2.84	3.98	0.023	Anorexia nervosa > control‡
Punishment sensitivity	13.15 ± 4.09	6.62 ± 4.14	4.04 ± 1.85	38.72	< 0.001	Anorexia nervosa > control§ Anorexia nervosa > recovered§ Recovered > control†
Intolerance of uncertainty	86.60 ± 16.22	55.17 ± 16.07	48.29 ± 12.34	39.90	< 0.001	Anorexia nervosa > recovered§ Anorexia nervosa > control§
EDI-2, body dissatisfaction	14.15 ± 8.01	8.54 ± 17.26	1.37 ± 2.14	7.19	0.002	Anorexia nervosa > control§ Recovered > control†
EDI-2, drive for thinness	12.80 ± 6.34	4.25 ± 4.50	0.75 ± 1.87	40.80	< 0.001	Anorexia nervosa > recovered§ Anorexia nervosa > control§ Recovered > control‡
Medication use, no.						
Antidepressant	7	5	0			
Antipsychotic	1	0	0			
Mood stabilizer	1	0	0			
Antidepressant and antipsychotic	1	0	0			
Antidepressant, antipsychotic and mood stabilizer	1	0	0			
Comorbid diagnoses, no.						
Major depressive disorder	3	3	0			
Anxiety disorder	4	4	0			
Major depressive disorder and anxiety disorder	6	2	0			

ANOVA = analysis of variance; BDI = Beck Depression Inventory; EDI-2: Eating Disorder Inventory-2; SD = standard deviation; STAI = State Trait Anxiety Inventory.
*Unless otherwise indicated.
†$p < 0.05$.
‡$p < 0.01$.
§$p < 0.001$.

Table 2: Group comparisons of network activity

Network; region; comparison	Model; *t* value, *p* value					
	Model 1*		Model 2†		Model 3‡	
Salience network						
Anterior cingulate cortex						
Control > anorexia nervosa	4.59	0.030	4.42	0.002	3.85	< 0.001
Control > recovered	3.87	0.039	4.19	0.005	4.39	0.011
Default mode network						
Precuneus						
Control > anorexia nervosa	3.58	0.023	3.85	< 0.001	4.91	0.013
Sensorimotor network						
Left postcentral gyrus						
Control > anorexia nervosa	5.26	0.028	5.42	0.013	4.40	0.005
Control > recovered	4.51	0.06	4.81	0.026	4.22	0.024
Right postcentral gyrus						
Control > anorexia nervosa	5.03	0.002	5.21	< 0.001	—	
Recovered > anorexia nervosa	4.50	0.008	4.43	0.008	—	
Supplementary motor area						
Control > anorexia nervosa	4.64	0.008	4.91	0.002	—	
Recovered > anorexia nervosa	4.46	0.019	4.53	0.018	—	

*Model 1: covarying for age, body mass index, Beck Depression Inventory score, State Trait Anxiety Inventory score, psychiatric medication use (yes/no).
†Model 2: covarying for the same as Model 1, excluding medication use.
‡Model 3: no covariates.

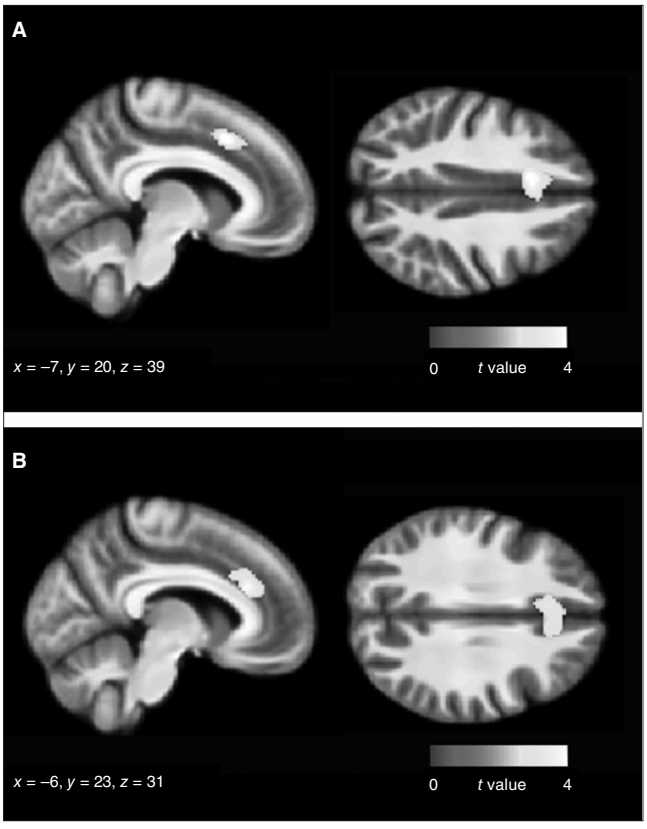

Fig. 1: Contrast of salience network activity in **(A)** control women compared with women with anorexia nervosa (control > anorexia nervosa) and **(B)** control women compared with recovered women (control > recovered). Data are shown in the radiologic convention on a group average anatomic image; cluster $p < 0.01$ false-discovery rate–corrected.

Correlations between fMRI and behavioural data

For correlations between fMRI and behavioural data, *z* scores reflecting network activity for each participant were extracted at the local maxima for the region of interest in each network (Montreal Neurological Institute coordinates were *x*, *y*, z = 0, –66, 30 in the DMN/precuneus; *x*, *y*, *z* = –8, 16, 42 in the SN/ACC; *x*, *y*, *z* = –42, –16, 38 in the SMN/LPG; *x*, *y*, *z* = 48, –14, 36 in the SMN/RPG; and *x*, *y*, *z* = 14, –6, 66 in the SMN/SMA).

In control women, there was a significant correlation between SN activity and both sensitivity to reward ($r = –0.63$, $p = 0.003$) and sensitivity to punishment ($r = –0.55$, $p = 0.013$), with greater activity associated with reduced scores. In control women, there was also a significant correlation between SMN activity (SMA) and both body dissatisfaction ($r = –0.51$, $p = 0.021$) and sensitivity to punishment ($r = –0.65$, $p = 0.002$), and between SMN activity (LPG) and sensitivity to reward ($r = –0.47$, $p = 0.035$), with greater SMN activity associated with reduced scores. In recovered women, greater SN activity was associated with greater harm avoidance ($r = 0.48$, $p = 0.038$). In addition, greater DMN activity in recovered women was associated with lower IU scores ($r = –0.55$, $p = 0.014$). Greater activity in the SMN (LPG) was also associated with lower IU scores in recovered women ($r = –0.47$, $p = 0.037$). No significant correlations between network activity and behavioural measures were observed for women with anorexia nervosa.

Discussion

To our knowledge, this study is the first to investigate DMN and SN activity in women with anorexia nervosa and to compare this activity between women with anorexia and recovered women. Both women with anorexia and recovered

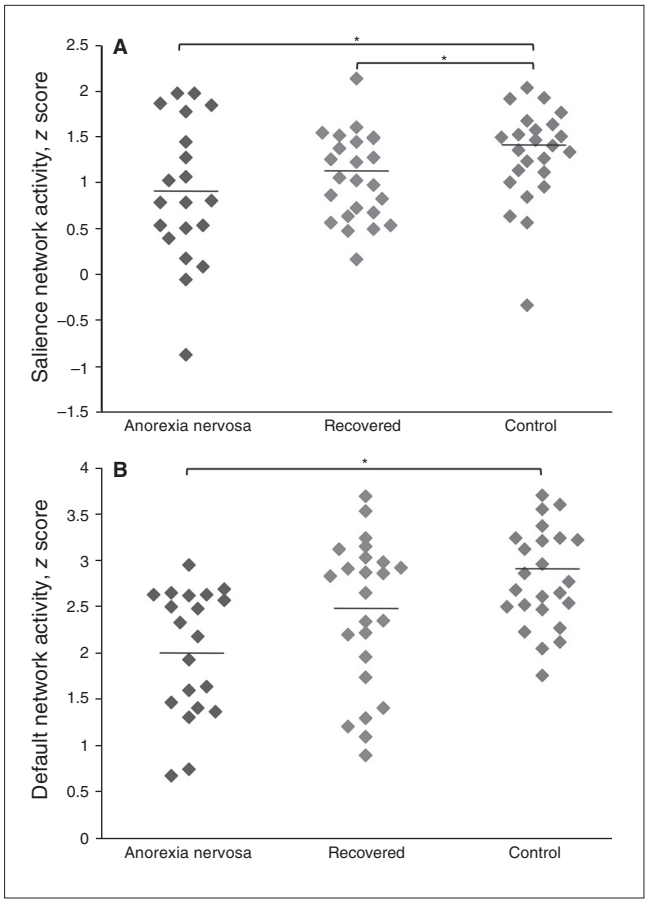

Fig. 2: Activity in the **(A)** salience network (SN) and **(B)** default mode network (DMN) for individual participants in each group. The *z* scores reflect activity at the local maxima for the DMN (precuneus) and SN (anterior cingulate cortex). Group comparison significance levels reflect SPM *t* contrasts, which include multiple comparison correction (see the Methods section). Lines indicate group means. *$p < 0.05$.

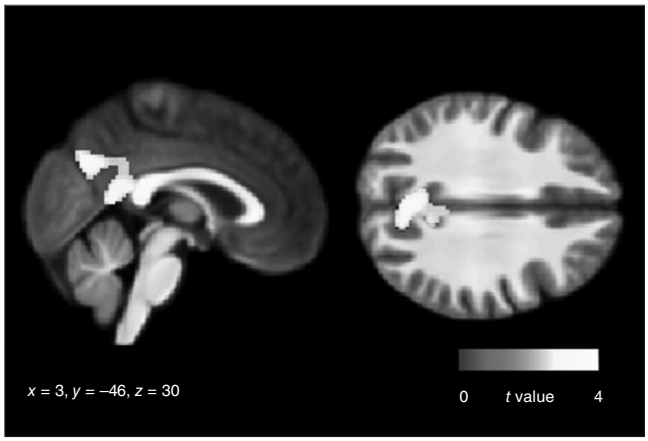

Fig. 3: Contrast of default mode network activity in control women compared with women with anorexia nervose (control > anorexia nervosa). Data are shown in the radiologic convention on a group average anatomic image; cluster $p < 0.01$ false-discovery rate–corrected.

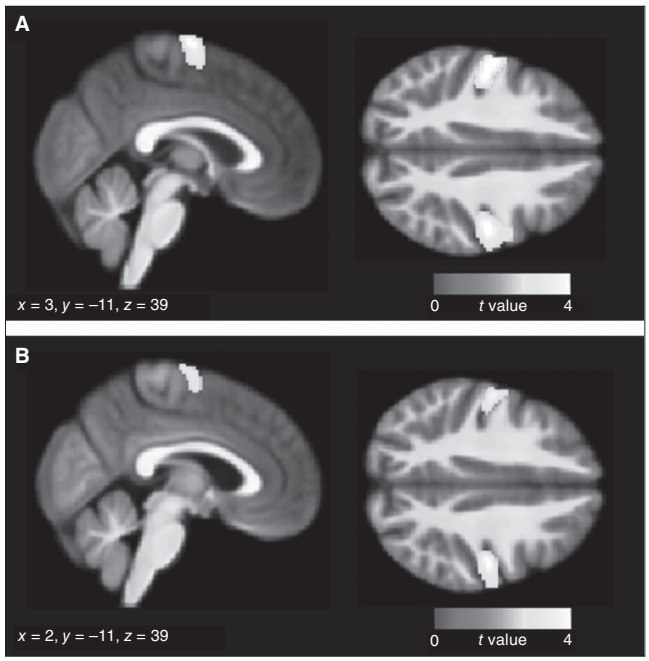

Fig. 4: Contrast of sensorimotor network activity in **(A)** control women compared with women with anorexia nervosa (control > anorexia nervosa) and **(B)** recovered compared with ill women (recovered > anorexia nervosa). Data are shown in the radiologic convention on a group average anatomic image; cluster $p < 0.01$ false-discovery rate–corrected.

women showed significantly decreased intrinsic SN activity in the ACC. In the DMN, those with anorexia showed significantly decreased activity in the precuneus. In addition, women with anorexia showed significantly reduced activity in the SMN compared with both controls and recovered women. The recovered women showed only a marginal reduction in this network compared with controls. Altered SN activity in women with anorexia and those who recovered from the disease suggests that alterations in salience or reward processing circuits could be a trait abnormality. Reduced DMN and SMN activity in women with anorexia seems to be a marker of illness state.

The SN-relevant brain regions are the insula and the ACC.[20] The main insula functions in the SN are detection and response to salient stimuli, whereas the ACC is important for motor response and for directing attention to reward and dopamine (DA)-related learning signals.[51,52] The ACC has also been linked to processing taste reward[53] and the hedonic properties of food[54] and to self-referential processing,[55] including body image perception in women with anorexia nervosa.[56] Altered ACC activation has previously been found in this population,[2,4,6,10] and our results further support this area contributing to the behaviour of individuals with anorexia nervosa. The difference in ACC activity between controls and women with anorexia nervosa was slightly more posterior than that between controls and recovered women, but both result regions were close and part of the cognitive ACC.[57] In light of the ACC's function of orienting to homeostatically relevant stimuli[20] and contribution to DA-related learning and

action selection,[51,52] altered activity in women with anorexia nervosa could be related to difficulty in responding to nutritional needs and to difficulties in learning and behaviour modification. This idea would be consistent with the ability of individuals with anorexia nervosa to restrict food intake and with previously found learning inefficiencies in a DA-based learning paradigm in this population.[58] Reduced intrinsic ACC function in the SN could underlie aberrant motivational drives in individuals with anorexia nervosa, influencing such things as eating behaviours, reward processing and pathologic body perception.[6] In support of this idea, a previous study found reduced ACC activation in individuals with anorexia nervosa during self–other body comparison.[59] However, in the present study, we did not find a correlation between body dissatisfaction (EDI-2) and SN activation. Future studies should include additional body image measures to more thoroughly explore this association. The reason and underlying neurobiological mechanisms for reduced SN activity in individuals with anorexia nervosa and those recovered from the disease are unclear. However, since brain regions contributing to the SN show dopaminergic innervation, alterations in DA neuronal function in individuals with anorexia nervosa may contribute to altered SN activity or vice versa. Indeed, DA alterations previously have been associated with anorexia nervosa in both ill[8] and recovered[60] individuals.

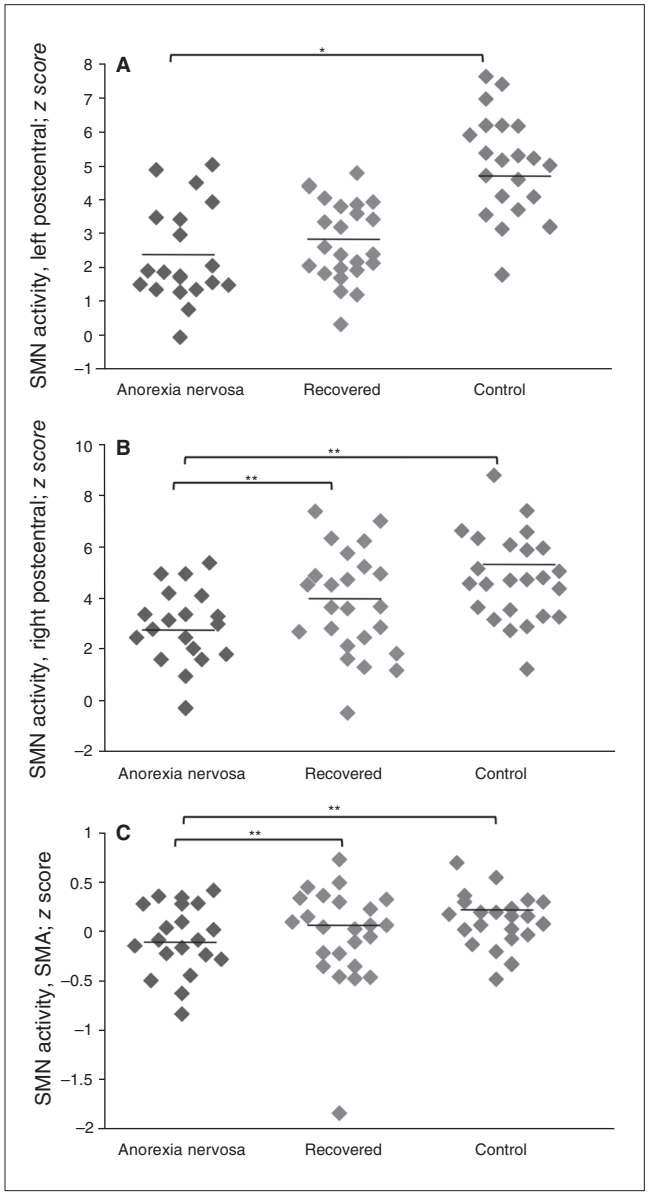

Fig. 5: Activity in the sensorimotor network (SMN) for individual participants in each group. The *z* scores reflect activity at the local maxima for the **(A)** left postcentral gyrus, **(B)** right postcentral gyrus, and **(C)** supplementary motor area (SMA). Group comparison significance levels reflect SPM *t* contrasts, which include multiple comparison correction (see the Methods section). Lines indicate group means. *$p < 0.05$, **$p < 0.01$.

That women with anorexia nervosa and recovered women showed similar alterations in this network may point to a trait abnormality, although an illness effect cannot be excluded. Supporting this idea, previous studies have suggested that SN abnormalities reflect trait vulnerabilities in patients with other psychiatric disorders.[61] It is possible that homeostatic awareness and intrinsic reward circuit function are altered in individuals with anorexia nervosa premorbidly, which could predispose to the illness. It is of note that in control women, higher reward and punishment sensitivity scores were associated with reduced SN activity. Women with anorexia nervosa and recovered women both had reduced SN activity and greater punishment sensitivity scores than controls; women with anorexia also had greater reward sensitivity than controls. This supports a link between SN activity and reward processing and, although speculative, suggests that controls at the high end of these scores may have shown reward processing dysfunction in the SN in the direction of the patient groups, albeit to a lesser extent. This association was not observed in women with anorexia nervosa or recovered women, potentially further supporting the theory of dysfunctional reward networks in individuals with anorexia nervosa.[6,8] In recovered women, the positive association between harm avoidance and ACC activity seems counterintuitive, since one would expect the closer brain activation is to controls, the more normal (and therefore lower) harm avoidance scores would be. This result needs replication and further study, but may point to altered brain activity related to often premorbid anxiety in individuals with anorexia nervosa.

Women with anorexia nervosa may have an altered sense of self-awareness, contributing to body image distortion, ability to starve themselves and lack of recognition of starvation consequences.[6,33,59,62] The reduced DMN activity we observed in the present study may reflect this alteration. The DMN is thought to support self-related cognitive activities.[22] The precuneus, a core component of the DMN, plays an important role in these processes.[55] Altered precuneus activation has previously been observed in individuals with anorexia nervosa during self-image viewing,[33] and precuneus grey matter decreases have also been demonstrated in this population,[49] supporting the idea that this area contributes to core anorexia nervosa symptoms.[63] Serotonin 1A receptor activity has been shown to inversely predict DMN

activation,[64] and increased serotonin 1A receptor availability has been associated with anorexia nervosa in ill,[65] but not recovered, individuals.[66] Thus, while speculative, alterations in this neurotransmitter system could be related to reduced DMN activity in individuals with anorexia nervosa but not in those recovered from the disease, suggesting that this abnormality is related to the illness state. Such a pattern of possible state-related abnormalities in psychiatric populations has been suggested previously.[67–69]

Women with anorexia nervosa and recovered women showed typical demographic and behavioural results and, as found previously, women with anorexia nervosa had increased IU scores.[70] Recovered women showed a tendency toward increased IU scores compared with controls. However, greater DMN activity was associated with lower IU scores in recovered women and, although speculative, DMN activity could be related to IU scores as a biologic trait of anorexia nervosa. With weight loss and state-dependent increase in IU scores, this association may become unhinged.

We were primarily interested a priori in the SN and DMN, but we also investigated the BGN and SMN, as post hoc analyses revealed these networks to be highly correlated with the task. A previous analysis of data from the same anorexia nervosa and control samples included in the present study (compared with obese individuals) revealed greater responsiveness in women with anorexia nervosa than controls in the putamen in both positive and negative prediction error conditions.[8] The present analysis revealed no group differences in the BGN. Possible associations between intrinsic and task-specific activation need further exploration.

Similar to DMN and SN activity, SMN activity was reduced in women with anorexia nervosa compared with controls. This reduction was only marginal when comparing recovered women with controls. Furthermore, women with anorexia nervosa demonstrated reduced SMN network activity compared with recovered women. This suggests alterations in this network may also be related to illness state. That SMN activity was most correlated to the task is not surprising, as it involved receiving sensory stimulation (fluid in the mouth). Reduced SMN activity in women with anorexia nervosa corresponds with previous findings of reduced somatosensory responsiveness in this population.[71] Our previous study of task-related responses during this sensory stimulation task found reduced SMA activity in women with anorexia nervosa compared with controls during both sucrose expectation and unexpected sucrose omission.[8] In addition, the increased SMN activation we observed in recovered women compared to those with anorexia corresponds with a previous finding of increased regional cerebral blood flow in the RPG in women with anorexia nervosa after, compared to before, treatment-related weight gain.[72] Favaro and colleagues[38] have suggested that SMN impairments in individuals with anorexia nervosa reflect dysfunctional processing of somatosensory information regarding body size perception. They found a significant correlation between body image measures and SMN activation. However, they found women with anorexia nervosa to have SMN hyperconnectivity. The reason for this discrepancy between studies is unclear, but could be owing to differences between intrinsic measures at rest compared with those across task (although studies suggest the 2 measures should be similar[12–15,18,19]), differences in inclusion criteria (no participant with anorexia nervosa in the present study reported any binge eating or purging behaviours, whereas 5 participants in the study by Favaro and colleagues did report such behaviours) or methodological differences. For example, Favaro and colleagues determined networks based on group ICA in controls alone, whereas we conducted ICA across all groups. In addition, while the "somatosensory" network referred to in the study by Favaro and colleagues includes many of the same areas as the "sensorimotor" network in our study, the 2 are not identical. Interestingly, Favaro and colleagues also found recovered women to demonstrate potential network recovery, as these women did not show the hyperconnectivity seen in those with anorexia nervosa. Although additional studies will be necessary to clarify directionality, both studies suggest SMN abnormalities to be state- rather than trait-related.

Similar to SN activity, there was a negative correlation between SMN activity and sensitivity to punishment in control women. As noted for the SN, this could indicate that controls with greater sensitivity to punishment, more in the direction of anorexia nervosa, also have network activity in the direction of anorexia nervosa (i.e., reduced), although this is speculative. In addition, greater body dissatisfaction was associated with reduced SMN activity in control women. This also suggests that control women who were behaviourally similar to women with anorexia nervosa showed network activity similar to those with anorexia nervosa. Finally, there was an association between lower IU scores and greater SMN activity in recovered women, similar to that in the DMN in these women. Given that recovered women had greater SMN activity than those with anorexia nervosa, this could reflect women with greater recovery having both reduced IU scores and increased SMN activity (more similar to controls than women with anorexia nervosa).

The present study complements recent reports of altered network activity in individuals with anorexia nervosa. In addition to finding somatosensory hyperconnectivity in the anorexia nervosa group, Favaro and colleagues[38] also found reduced ventral visual network activity in both ill and recovered women. They suggest these alterations may reflect dysfunctional integration of visual and somatosensory information, potentially underlying body image disturbances. Previous studies have also suggested that alterations in areas in the DMN and SN contribute to impaired body image perception.[33,59,62] Sachdev and colleagues[33] found patients with anorexia nervosa to show greater activation of areas in both the DMN and SN during self-image viewing, although they showed similar activation to controls while viewing images of other people. However, the present study found a significant association only between the measure of body image used (body dissatisfaction from the EDI-2) and SMN, and this association was seen only in control women. Future studies

should include multiple measures of body image to assess these associations in more detail.

Cowdrey and colleagues[39] reported increased activation within the DMN in the precuneus and DLPFC in recovered women. A disparity between their finding and our results is that while their findings suggest increased DMN activity in recovered women, we found decreased activity in women with anorexia nervosa and no difference in recovered women compared with controls. Cowdrey and colleagues suggest their findings indicate that DMN abnormalities are trait-related. However, as they did not include a currently ill group, it is unclear how to reconcile their findings with those of the present study, which suggest that DMN impairments are state-dependent. There are a number of possible reasons for this discrepancy: methodological differences (e.g., regions included in the DMN, number of components used in the ICA, groups included in determination of components, analytic methods, intrinsic activity at rest or across task) and patient population differences (e.g., fewer participants in the study by Cowdrey and colleagues, some of whom had a lifetime history of bulimia nervosa; length of illness duration; recovery duration). Future studies of anorexia nervosa before and after recovery can help determine whether DMN alterations are state- or trait-dependent.

Limitations

A possible limitation of the present study is the inherent group differences. As depression is commonly comorbid with anorexia nervosa, it is not surprising that women with anorexia nervosa had significantly higher depression scores than those in the other groups. Similarly, both ill and recovered women had higher anxiety scores than controls. To control for those potential confounds, we included depression (BDI) and anxiety (STAI) scores as covariates in the model, so it is less likely that the reduced network activity seen in anorexia nervosa was simply due to depression or anxiety. There was also an expected group difference in BMI (lower in women with anorexia nervosa than recovered and control women). In addition, women with anorexia nervosa were younger than recovered and control women, leading to a corresponding difference in education. Also, more ill and recovered women than controls were taking psychiatric medications. We also included these potential confounds as covariates. Despite those efforts, we cannot exclude potential effects of those variables, but we believe we minimized such effects. We should also note that the high variability in body dissatisfaction in recovered women suggests that there is persistent psychopathology in some participants; all individuals were recovered according to DSM criteria, but there may have been participants who were, from a cognitive standpoint, less recovered than others. However, our finding of similarities in SN and differences in DMN activity between women with anorexia nervosa and recovered women may suggest biologic underpinnings that are not simply due to anorexia nervosa–related cognition. Differences in grey matter volume have also been demonstrated in individuals with anorexia nervosa,[49] which could contribute to functional differences. To assess this, we performed structural analyses and found no group differences in total grey or white matter volume or in total intracranial volume. While a recent publication has detailed group differences in some regions in this sample,[73] there was no overlap between regions reported to have group differences here and those demonstrating volumetric group differences. As such, it is unlikely that structural differences contributed to functional effects. Another potential limitation may be sample size. Although we had sufficient power to identify group differences in intrinsic network activity (the main purpose of the analysis), the study may have been underpowered to detect group differences investigated in our exploratory analysis of task condition–related network modulation. A future study designed to address this question with a larger sample size may identify group differences.

Conclusion

Our findings suggest that anorexia nervosa and recovery from the disorder are associated with altered intrinsic activity in the SN and that current anorexia nervosa is associated with altered intrinsic activity in the DMN and SMN. To our knowledge, in addition to being the first study to investigate the DMN in currently ill women with anorexia nervosa, this is also the first study to investigate the SN and DMN in both anorexia nervosa and recovered populations. This allowed us to identify potential effects of illness state versus trait on activity in these functionally connected networks. As reduced SN activity was observed in both ill and recovered women, this suggests network alterations are due to more than physiologic effects of being currently ill. However, it is unknown if this reflects a scar of the illness state or a trait vulnerability present before symptom onset. Because altered DMN and SMN activity were only observed in currently ill and not in recovered women, this suggests alterations in these networks may be a state marker that normalizes with recovery. As such, it is possible that normalization of intrinsic network activity could be used as a marker of treatment-related improvement. Future studies will be needed to investigate intrinsic network activity in individuals with anorexia nervosa before and after treatment to further assess this possibility.

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